J|A|C|S
COMMUNICATIONS

Gold(III)-Catalyzed Nitrene Insertion into Aromatic and Benzylic C−H Groups

Zigang Li, David A. Capretto, Ronald O. Rahaman, and Chuan He*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

Received April 5, 2007; E-mail: chuanhe@uchicago.edu

Gold-catalyzed reactions have received increased attention in the past few years. A variety of organic transformations have been shown to be mediated by gold(I) or gold(III) complexes in solution.[1] In addition to its superb ability to activate alkyne and related substrates,[2] gold(III) is also capable of electrophilically metallating aromatic C−H groups to afford arylgold(III) species; this activity has been utilized to induce C−C bond formations.[3] We report here a process to form C−N bonds from direct functionalization of aromatic or benzylic C−H groups catalyzed by $AuCl_3$ at room temperature.

Direct functionalization of inert C−H bonds is highly valued in chemical synthesis.[4,5] However, there are few methods that can achieve direct nitrene insertion into aromatic C−H bonds. Che et al. have utilized neighboring groups to direct a palladium-catalyzed C−N bond formation using persulfate as the oxidant, while Yu et al. reported a copper−catalyzed transformation with similar substrates.[6] In addition, Pérez et al. have reported a case of benzene amination mediated by a copper−based catalyst with the use of PhI═NTs.[7] In the latter case, if benzene is replaced by toluene, the reaction occurs solely on the benzylic position. We and others have recently developed nitrene transfer catalysts for olefin aziridination as well as intra− and intermolecular amination of aliphatic C−H bonds.[5,8] However, none of these systems are successful in the intermolecular activation of aromatic C−H bonds.

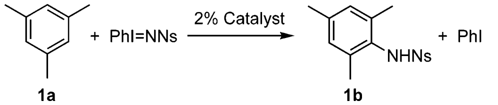
Since simple aromatic groups readily react with $AuCl_3$ to form arylgold(III) species and 1 equiv of HCl at room temperature, we hypothesized that the in situ generated arylgold(III) might react with an electrophilic nitrogen source to induce C−N bond formation. Thus, we tested reactions of mesitylene with various nitrogen sources with $AuCl_3$ (2%) as the catalyst. To our delight, with PhI═NNs (Ns = *p*-nitrosulfonyl which can be readily deprotected from the product), an efficient reaction occurred to give the aromatic C−N formation product in 90% yield at room temperature (entry 5, Table 1). The high efficiency of the reaction (based on PhI═NNs; mesitylene was used in excess) was surprising given the mild reaction conditions employed. Other metal salts or HCl failed to mediate the same reaction at room or higher temperatures (Table 1).

More substrates were tested and results are listed in Table 2. Reaction yields ranged from good to excellent and chemoselectivities were excellent for methyl-substituted benzenes. We found tri- or more substituted benzenes could undergo the reaction at room temperature with 1−2% $AuCl_3$. However, less substituted benzenes and benzene itself yielded less than 5% product under the same conditions. This is a reaction pattern we have yet to fully understand.[3f−i]

When 1,3,5-triethylbenzene was used as the substrate we observed a trace amount of benzylic amination (entry 6, Table 2), which prompted us to test substrates with more activated benzylic C−H bonds. With tetrahydronaphthalene and indan, in addition to aromatic C−H insertion, high percentages of benzylic nitrene insertion were observed (eq 2, Figure 1). To further confirm this activity, we performed a reaction with 1,3,5-triisopropylbenzene. We obtained a mixture of aromatic and aliphatic nitrene insertion products with a ratio of 1:1.5 (eq 3, Figure 1). Thus, the current system can also mediate benzylic C−H amination if weak C−H bonds are present. However, *this system shows good chemoselectivity toward aromatic C−H bonds over primary and secondary benzylic C−H bonds, a unique and rarely observed property*.

What is the mechanism of the unique C−H nitrene insertion observed in the current system? Simple Lewis acid-based chemistry with gold(III) activating PhI═NNs could be excluded since other metal ions and HCl were not effective and electron rich heterocycles such as indoles and furans showed no reactivity under the same reaction conditions. To gain insight into the mechanism, a reaction was carried out with a 1:1 mixture of mesitylene and mesitylene-d^{12} with PhI═NNs and $AuCl_3$. ^1H NMR showed a 1:1 product distribution, suggesting that the C−H functionlization step might not be rate determining (eq 4, Figure 1). A second experiment was

Table 1. Effects of Metal Complexes and Reaction Conditions[a]

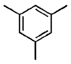
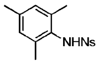
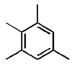
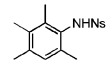
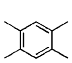
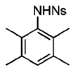
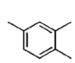
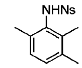
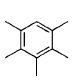
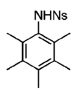
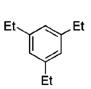
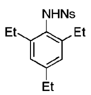


1a **1b** (1)

entry	catalyst	solvent	temp (°C)	yield (%)
1	$AuCl_3$	CH_3CN	r.t. and 50	trace[b]
2	$AuCl_3$	THF	r.t. and 50	trace[b]
3	$AuCl_3$	CCl_4	r.t.	trace[b]
4	$AuCl_3$	CCl_4	50	>75%[c]
5	$AuCl_3$	CH_2Cl_2	r.t.	90%[c]
6	$PdCl_2$	CH_2Cl_2	r.t. and 50	no **1b**[b]
7	$ZnCl_2$	CH_2Cl_2	r.t. and 50	no **1b**[b]
8	$FeCl_2$	CH_2Cl_2	r.t. and 50	no **1b**[b]
9	$Cu(OTf)_2$	CH_2Cl_2	r.t. and 50	trace[b]

[a] All reactions were carried out using 50 mg PhI═NNs in 4 mL solvent at a ratio of mesitylene/PhI═NNs = 8:1. Lower conversion under solventless conditions; r.t. = room temperature. [b] Determined by ^1H NMR. [c] Isolated yield.

Table 2. $AuCl_3$−Catalyzed Nitrene Insertion into Aromatic C−H Groups[a]

Entry[a]	Substrate	Product	Yield(%)[b]	Entry[a]	Substrate	Product	Yield(%)[b]
1			90	4			75
2			67	5			73[c]
3			61	6			70[d]

[a] All reactions were carried out by using 50 mg PhI═NNs in 4 mL solvent at a ratio of hydrocarbons/PhI═NNs = 8:1. [b] Isolated yield. [c] All three products with a ratio of 1:1:1 based by ^1H NMR. [d] With <5% of benzylic nitrene insertion based on ^1H NMR.

10.1021/ja0724137 CCC: $37.00

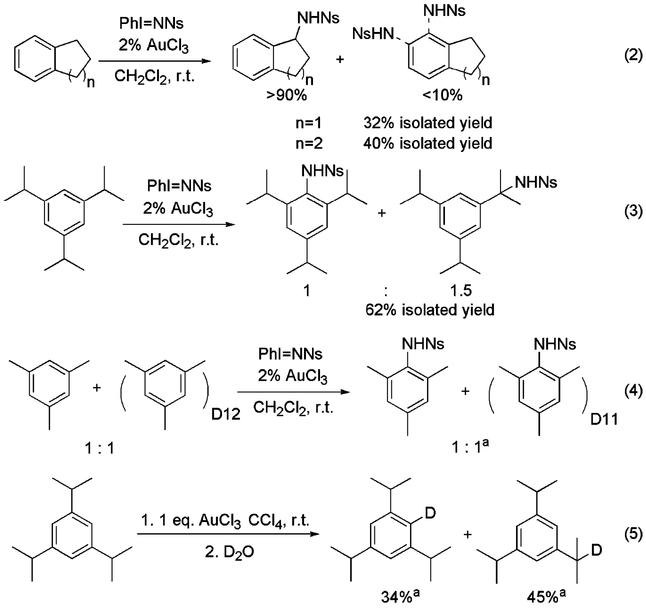
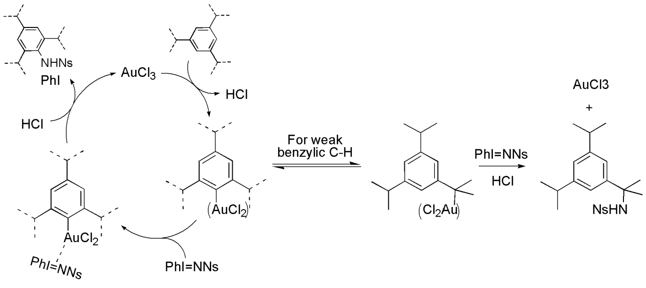


Figure 1. Amination of benzylic C−H groups catalyzed by AuCl$_3$ and isotope labeling experiments. ^{a} ^{1}H NMR ratio and conversion.

Scheme 1



performed with 1,3,5-triisopropylbenzene and a stoichiometeric amount of AuCl$_3$ in CCl$_4$. The reaction was quenched with D$_2$O after several hours and analyzed by ^{1}H NMR, which showed disappearance of proton signal from both the aromatic and benzylic positions (eq 5, Figure 1).[9] These results suggest activation of the benzylic protons by gold(III), resulting in H−D scrambling.

We propose a mechanism (Scheme 1) to account for the observed reactivity pattern. First, the arylgold(III) species is generated from the reaction of AuCl$_3$ and an aromatic C−H bond.[3] PhI=NNs is then activated by interaction with the gold(III) center. This activiation leads to attack on the carbon of the arylgold(III) species resulting in product and the formation of AuCl$_3$. This mechanism helps to explain the unique chemoselectivity of this reaction; formation of the arylgold(III) species is key and required for the selective aromatic C−H nitrene insertion. In the presence of very weak benzylic C−H bonds, our isotope experiment (eq 5) suggests that gold(III) displaces a weak benzylic proton to form a carbon−gold(III) bond, which subsequently undergoes the nitrene insertion (Scheme 1). Arylgold(III) may form first before gold(III) migrates to the benzylic position. Formations of benzylic−gold species are known and have been reported in the past.[10] Although other mechanistic possibilities cannot be excluded at this time, our experiments suggest that a nearby aromatic C−H is required for the benzylic C−H amination to occur.[11]

In closing, we report here a gold-catalyzed nitrene insertion into aromatic and benzylic C−H bonds at room temperature. Currently, this chemistry has a narrow scope limited to simple arenes, but the unique activity and chemoselectivity present intriguing mechanistic questions. Further studies of these transformations may lead to new paths for developing efficient C−H activation methodologies and a better understanding of both gold chemistry and C−N bond formation processes.

Acknowledgment. This research was supported by the Alfred P. Sloan Foundation and the University of Chicago.

Supporting Information Available: Experimental details and supplemental figures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65. (b) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200−203. (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936. (d) Gorin, D. J.; Toste, F. D. *Nature*, **2007**, *446*, 395−403.

(2) (a) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921−10925. (b) Wei, C.-M.; Li., C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584−9585. (c) De Vos, D. E.; Sels, B. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 30−32. (d) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526−4527. (e) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807. (f) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500−10501.

(3) (a) Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053−3059. (b) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288. (c) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, *18*, 3485−3496. (d) Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli. F. *Synlett* **2004**, 944−950. (e) Luo, Y.; Li, C.-J. *Chem. Commun.* **2004**, 1930−1931. (f) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669−3671. (g) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964−5965. (h) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596−13597. (i) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049−5054.

(4) (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586. (b) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518−3520. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72. (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439−2463. (e) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (f) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634−12635.

(5) (a) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184−5186. (b) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120−9132. (c) Espino, C. J.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379. (d) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641−4644. (e) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30−34. (f) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639−642. (g) A very recent paper on intramolecular activation of aromatic C−H bonds with acrylate azides: Stokes, B, J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500−7501.

(6) (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049. (b) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790−6791.

(7) (a) Díaz-Requejo, M. M.; Belderraín, T. R.; Carmen-Nicasio, M.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078−12079. (b) Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784−11791.

(8) (a) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202−16203. (b) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212. (c) Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876−5880.

(9) After mesitylene-d^{12} was treated with a stoichiometeric amount of AuCl$_3$ in CCl$_4$ at room temperature for several hours the reaction was quenched with water. We detected the H−D exchange for both aromatic and benzylic protons with exchange predominantly occurring on the aromatic position. We then tested triisopropylbenzene and quantified the H−D exchange ratio by ^{1}H NMR. Please see Supporting Information for details.

(10) (a) Bennett, M. A.; Hoskins, K.; Kneen, W. R.; Nyholm, R. S.; Mason, R.; Hitchcock, P. B.; Robertson, G. B.; Towl, A. D. C. *J. Am. Chem. Soc.* **1971**, *93*, 4592−4593. (b) Parish, R. V. *Gold Bull.* **1997**, *30*, 3−12.

(11) We prepared pentamethylisopropylbenzene in a 1:1 mixture with pentamethylbenzene. This mixture was subjected to the amination reaction, and the benzylic insertion for the fully substituted pentamethylisopropylbenzene was not detected. Also, 1,4-diisopropylbenzene only gave trace amount of products.

JA0724137